10/625059 02-13-08 C of C

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No.: 7,291,603 B2 (U.S. application no. 10/625,059, filed July 22, 2003)

Issued: November 6, 2007

Inventor(s): Wilde et al.

For: NUCLEOSIDE COMPOUNDS AND THEIR USE FOR TREATING CANCER AND DISEASES ASSOCIATED WITH SOMATIC MUTATIONS

Attorney Docket No.: 10589-015-999
(CAM: 109843-999014)

REQUEST FOR CERTIFICATE OF CORRECTION UNDER 37 C.F.R. §1.322

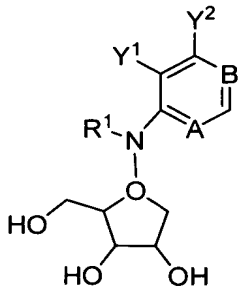
Attention Certificate of Correction Branch
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

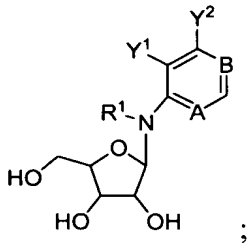
Patentee hereby respectfully requests the issuance of a Certificate of Correction in connection with the above-identified patent. The correction is listed on the attached Form PTO-1050.

The errors were made by the United States Patent and Trademark Office ("USPTO") in connection with the above patent, wherein at:

claim 1, column 86, lines 40-54, please replace the structure:

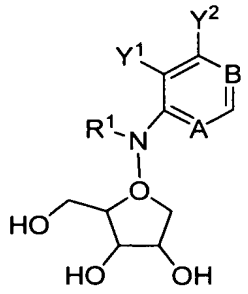


with the structure:

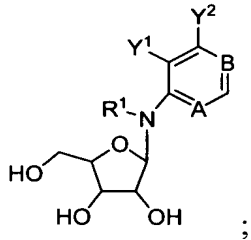


;

claim 5, column 88, lines 1-15, please replace the structure:

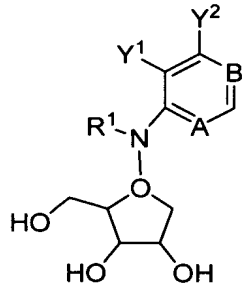


with the structure:

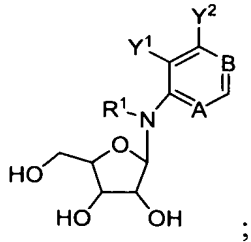


;

claim 12, column 89, lines 45-58, please replace the structure:

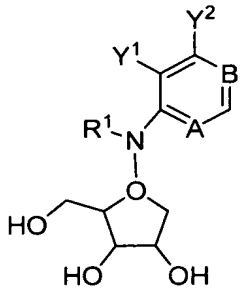


with the structure:

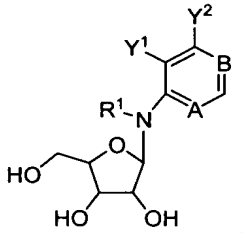


; and

claim 15, column 91, lines 1-15, please replace the structure:



with the structure:



Enclosed is a copy of a Reply to Office Action Under 37 C.F.R. § 1.111 filed in the USPTO in connection with the above-identified patent application on April 19, 2007 (the "Reply") evidencing the corrections in issued claims 1, 5, 12 and 15 (*i.e.*, claims 1, 9, 16 and 19 in the Reply) as set forth above. Further enclosed is a copy of a return-receipt postcard and Express Mail Receipt evidencing receipt of the Reply by the USPTO on April 19, 2007.

No fee is believed to be due in connection with this request since the errors were made by the USPTO. Should any fees be required, however, please charge such fees to Jones Day Deposit Account No. 50-3013. Please issue a certificate of correction as soon as possible.

Respectfully submitted,

Anthony M. Insogna, Reg. No. 35,203

By: Michael J. Bruner, Reg. No. 47,458

Date: February 11, 2008

By: Michael J. Bruner (Reg. No. 47,458)
JONES DAY
222 East 41st Street
New York, New York 10017
(212) 326-3939

For: Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
12750 High Bluff Drive, Suite 300
San Diego, California 92130
(858) 314-1130

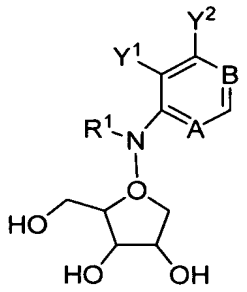
PRINTER'S TRIM LINE

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

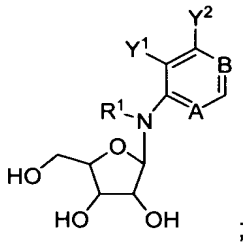
PATENT NO. : 7,291,603 B2
DATED : November 6, 2007
INVENTOR(S) : Wilde et al.

It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

claim 1, column 86, lines 40-54, please replace the structure:



with the structure:



;

MAILING ADDRESS OF SENDER:
JONES DAY
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(858) 314-1130
ATI-2308526v1
FORM PTO 1050

PATENT NO. 7,291,603 B2

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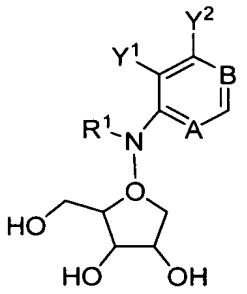
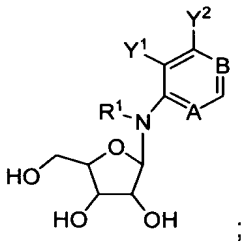
UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

claim 5, column 88, lines 1-15, please replace the structure:



with the structure:



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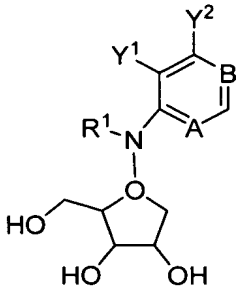
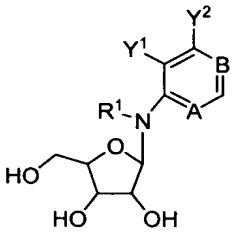


with the structure:



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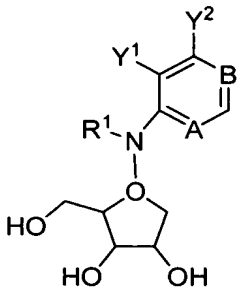
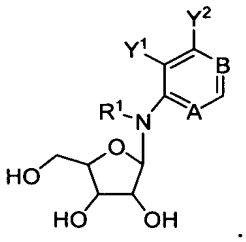
claim 15, column 91, lines 1-15, please replace the structure:



with the structure:



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Express Mail No EV 811 559 747US
Date Mailed April 19, 2007
Serial No. 10/625,059 Filed July 22, 2003
inventor Wilde et al.
For NUCLEOSIDE COMPOUNDS AND THEIR USE FOR TREATING CANCER AND DISEASES ASSOCIATED WITH SOMATIC MUTATIONS

☒ Reply to Office Action Under 37 CFR § 1.111;
☒ Petition for Extension of Time Under 37 CFR § 1.136(a) for one month with provision for required fee (in duplicate);
☒ Fee by Deposit Account 50-3013.

File no.: 10589-015-999 (CAM: 109843-999014) Sender: AMI//MLB

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Patent Publication
FEB 15 2008

Express Mail No. EV 811 559 747 US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Wilde et al.	Confirmation No.: 8259
Application No.: 10/625,059	Group Art Unit: 1623
Filed: July 22, 2003	Examiner: Olson, Eric
For: NUCLEOSIDE COMPOUNDS AND THEIR USE FOR TREATING CANCER AND DISEASES ASSOCIATED WITH SOMATIC MUTATIONS	Attorney Docket No.: 10589-015-999 CAM: 109843-999014

REPLY TO OFFICE ACTION UNDER 37 C.F.R. § 1.111

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This responds to the Office Action mailed December 21, 2006 in connection with the above-identified application. Applicants submit herewith a Petition for Extension of Time Under 37 C.F.R. § 1.136(a) for one (1) month with provision for the required fee (in duplicate).

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

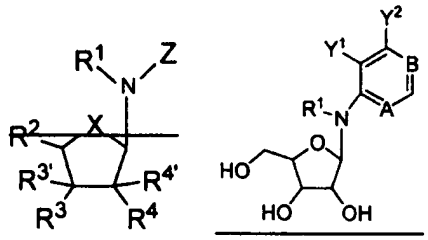
Remarks begin on page 13 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

1. (Currently Amended) A method of treating ~~or preventing~~ a disease resulting from a somatic nonsense mutation in ~~DNA or RNA~~ the p53 gene comprising administering to a patient in need thereof an effective amount of a compound having the structure:



~~I~~

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, racemate or stereoisomer thereof, wherein:

~~Z is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl;~~

A and B are each independently CH or N;

Y^1 and Y^2 are each independently hydrogen, hydroxy, halogen, nitro, cyano, sulfate, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, alkoxy, alkylthioether, carboxyalkyl, carbonylalkyl, amino, $NR^5R^{5'}$, amido, or alkoxycarbonyl;

R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or

unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl; and

R^5 and $R^{5'}$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl,

~~R^2 is substituted or unsubstituted alkyl, carboxy, amido, acyl, alkylcarbonyl, halogen, a biohydrolyzable group, $OP(O)_3^{2-}$, $O[P(O)_3]_2^{3-}$, $O[P(O)_3]_3^{4-}$, N_3, $CH_2NR_6R_7$ or CH_2OR^6;~~

~~R^3, $R^{3'}$, R^4 and $R^{4'}$ are at each occurrence independently OR^7, OR^8, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted alkylcarbonyl, a biohydrolyzable group, or R^3 and R^4 taken together form a bond, or R^3 and R^4 taken together with the atoms to which they are attached form a substituted or unsubstituted heterocyclo, or R^3 and $R^{3'}$ and/or R^4 and $R^{4'}$ taken together with the carbon to which they are attached form C(=O); and~~

~~R^6, R^7 and R^8 are at each occurrence independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted alkylcarbonyl, a biohydrolyzable group, or R^3 and R^4 taken together with the atoms to which they are attached form a substituted or unsubstituted heterocyclo,~~

wherein groups that are substituted are substituted with one or more groups selected from alkyl, alkenyl, alkynyl, cycloalkyl, aroyl, halo, haloalkyl, haloalkoxy, hydroxy, alkoxy, alkylthioether, cycloalkyloxy, heterocylooxy, oxo, alkanoyl, aryl, arylalkyl, alkylaryl, heteroaryl, heteroarylalkyl, alkylheteroaryl, heterocyclo, aryloxy, alkanoyloxy, amino,

alkylamino, arylamino, arylalkylamino, cycloalkylamino, heterocycloamino, mono- and di-substituted amino, alkanoylamino, aroylamino, aralkanoylamino, thiol, alkylthio, arylthio, arylalkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, arylalkylthiono, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, alkoxycarbonyl and guanidino.

2. (Original) The method of claim 1, wherein the compound, or a pharmaceutically acceptable salt, hydrate, solvate, clathrate or stereoisomer thereof, is administered as a composition comprising the compound and a pharmaceutically acceptable carrier or diluent.

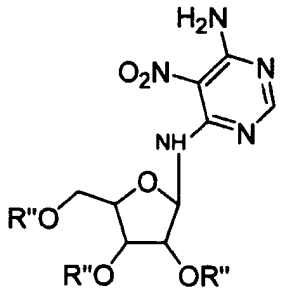
3. (Original) The method of claim 1, wherein the administration is intravenous.

4. (Canceled)

5. (Canceled)

6. (Canceled)

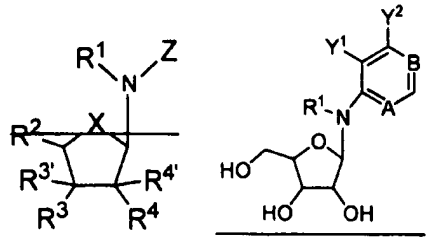
7. (Currently Amended) The method of claim 1, wherein the compound has the structure:



or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, racemate or stereoisomer thereof, wherein each occurrence of R'' is ~~independently~~ hydrogen~~, $OP(O_3)^{-2}$, $C(=O)CH_3$ or a biohydrolyzable group~~.

8. (Canceled)

9. (Currently Amended) A method of treating ~~or preventing~~ cancer associated with a nonsense mutation of the p53 gene in a human comprising administering to a human in need thereof an effective amount of a compound having the structure:



I

or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, racemate or stereoisomer thereof, wherein:

~~Z is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl;~~

A and B are each independently CH or N;

Y^1 and Y^2 are each independently hydrogen, hydroxy, halogen, nitro, cyano, sulfate, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, alkoxy, alkylthioether, carboxyalkyl, carbonylalkyl, amino, $NR^5R^{5'}$, amido, or alkoxycarbonyl;

R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl; and

R^5 and $R^{5'}$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl,

~~R^2 is substituted or unsubstituted alkyl, carboxy, amido, acyl, alkylcarbonyl, halogen, a biohydrolyzable group, $OP(O)_3^{2-}$, $O[P(O)_3]_2^{3-}$, $O[P(O)_3]_3^{4-}$, N_3, $CH_2NR_6R_7$ or CH_2OR^6;~~

~~R^3, $R^{3'}$, R^4 and $R^{4'}$ are at each occurrence independently OR^7, OR^8, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted alkylcarbonyl, a biohydrolyzable group, or R^3 and R^4 taken together form a bond, or R^3 and R^4 taken together with the atoms to which they are attached form a substituted or unsubstituted heterocyclo, or R^3 and $R^{3'}$ and/or R^4 and $R^{4'}$ taken together with the carbon to which they are attached form C(=O); and~~

~~R^6, R^7 and R^8 are at each occurrence independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted alkylcarbonyl, a biohydrolyzable group, or R^3 and R^4 taken together with the atoms to which they are attached form a substituted or unsubstituted heterocyclo,~~

wherein groups that are substituted are substituted with one or more groups selected from alkyl, alkenyl, alkynyl, cycloalkyl, aroyl, halo, haloalkyl, haloalkoxy, hydroxy, alkoxy, alkylthioether, cycloalkyloxy, heterocylooxy, oxo, alkanoyl, aryl, arylalkyl, alkylaryl, heteroaryl, heteroarylalkyl, alkylheteroaryl, heterocyclo, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, arylalkylamino, cycloalkylamino, heterocycloamino, mono- and di-substituted amino, alkanoylamino, aroylamino, aralkanoylamino, thiol, alkylthio, arylthio, arylalkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, arylalkylthiono, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, alkoxycarbonyl and guanidino.

10. (Original) The method of claim 9, wherein the administration is intravenous.

11. (Original) The method of claim 9, wherein the cancer is of the head and neck, eye, skin, mouth, throat, esophagus, chest, bone, blood, lung, colon, sigmoid, rectum, stomach, prostate, breast, ovaries, kidney, liver, pancreas, brain, intestine, heart or adrenals.

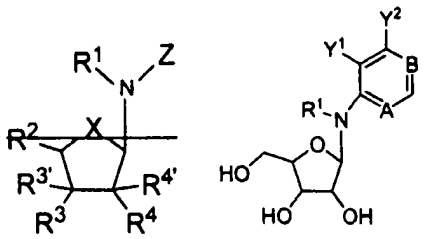
12. (Original) The method of claim 9, wherein the compound, or a pharmaceutically acceptable salt, hydrate, solvate, clathrate or stereoisomer thereof, comprises a pharmaceutically acceptable carrier or diluent.

13. (Original) The method of claim 9, wherein the cancer is a solid tumor.

14. (Original) The method of claim 9, wherein the cancer is sarcoma, carcinoma, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, Kaposi's sarcoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, retinoblastoma, a blood-born tumor or multiple myeloma.

15. (Original) The method of claim 9, wherein the cancer is acute lymphoblastic leukemia, acute lymphoblastic B-cell leukemia, acute lymphoblastic T-cell leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute monoblastic leukemia, acute erythroleukemic leukemia, acute megakaryoblastic leukemia, acute myelomonocytic leukemia, acute nonlymphocyctic leukemia, acute undifferentiated leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, or multiple myeloma.

16. (Currently Amended) A method of treating ~~or preventing~~ a disease associated with a nonsense mutation of the p53 gene comprising administering to a patient in need thereof an effective amount of a compound having the structure:



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or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, racemate or stereoisomer thereof, wherein:

~~Z is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl;~~

A and B are each independently CH or N;

Y^1 and Y^2 are each independently hydrogen, hydroxy, halogen, nitro, cyano, sulfate, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, alkoxy, alkylthioether, carboxyalkyl, carbonylalkyl, amino, $NR^5R^{5'}$, amido, or alkoxycarbonyl;

R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl; and

R^5 and $R^{5'}$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl,

~~R^2 is substituted or unsubstituted alkyl, carboxy, amido, acyl, alkylcarbonyl, halogen, a biohydrolyzable group, $OP(O)_3^{2-}$, $O[P(O)_3]_2^{3-}$, $O[P(O)_3]_3^{4-}$, N_3, $CH_2NR_6R_7$ or CH_2OR^6;~~

~~R^3, $R^{3'}$, R^4 and $R^{4'}$ are at each occurrence independently OR^7, OR^8, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted alkylcarbonyl, a biohydrolyzable group, or R^3 and R^4 taken together form a bond, or R^3 and R^4 taken together with the atoms to which they are attached form a substituted or unsubstituted heterocyclo, or R^3 and $R^{3'}$ and/or R^4 and $R^{4'}$ taken together with the carbon to which they are attached form C(=O); and~~

~~R^6, R^7 and R^8 are at each occurrence independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted alkylcarbonyl, a biohydrolyzable group, or R^3 and R^4 taken together with the atoms to which they are attached form a substituted or unsubstituted heterocyclo,~~

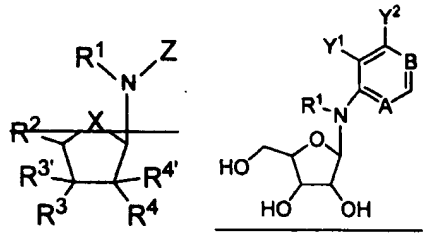
wherein groups that are substituted are substituted with one or more groups selected from alkyl, alkenyl, alkynyl, cycloalkyl, aroyl, halo, haloalkyl, haloalkoxy, hydroxy, alkoxy, alkylthioether, cycloalkyloxy, heterocylooxy, oxo, alkanoyl, aryl, arylalkyl, alkylaryl, heteroaryl, heteroarylalkyl, alkylheteroaryl, heterocyclo, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, arylalkylamino, cycloalkylamino, heterocycloamino, mono- and di-substituted amino, alkanoylamino, aroylamino, aralkanoylamino, thiol, alkylthio, arylthio, arylalkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, arylalkylthiono, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, alkoxycarbonyl and guanidino.

17. (Original) The method of claim 16, wherein the administration is intravenous.

18. (Original) The method of claim 16, wherein the disease is sarcoma, carcinomas, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma,

angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, Kaposi's sarcoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma or retinoblastoma.

19. (Currently amended) A method of inhibiting the growth of a cancer cell comprising contacting a cancer cell having a nonsense mutation in ~~its DNA or RNA~~ the p53 gene with an effective amount of a compound having the structure:



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or a pharmaceutically acceptable salt, hydrate, solvate, clathrate, racemate or stereoisomer thereof, wherein:

~~Z is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl;~~

A and B are each independently CH or N;

Y^1 and Y^2 are each independently hydrogen, hydroxy, halogen, nitro, cyano, sulfate, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo,

substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, alkoxy, alkylthioether, carboxyalkyl, carbonylalkyl, amino, $NR^5R^{5'}$, amido, or alkoxycarbonyl;

R^1 is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl; and

R^5 and $R^{5'}$ are each independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl,

~~R^2 is substituted or unsubstituted alkyl, carboxy, amido, acyl, alkylcarbonyl, halogen, a biohydrolyzable group, $OP(O)_3^{2-}$, $O[P(O)_3]_2^{3-}$, $O[P(O)_3]_3^{4-}$, N_3, $CH_2NR_6R_7$ or CH_2OR^6;~~

~~R^3, $R^{3'}$, R^4 and $R^{4'}$ are at each occurrence independently OR^7, OR^8, hydrogen, halogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted alkylcarbonyl, a biohydrolyzable group, or R^3 and R^4 taken together form a bond, or R^3 and R^4 taken together with the atoms to which they are attached form a substituted or unsubstituted heterocyclo, or R^3 and $R^{3'}$ and/or R^4 and $R^{4'}$ taken together with the carbon to which they are attached form C(=O); and~~

~~R^6, R^7 and R^8 are at each occurrence independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclo, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted arylcarbonyl, substituted or unsubstituted alkylcarbonyl, a biohydrolyzable~~

~~group, or R^3 and R^4 taken together with the atoms to which they are attached form a substituted or unsubstituted heterocyclo,~~

wherein groups that are substituted are substituted with one or more groups selected from alkyl, alkenyl, alkynyl, cycloalkyl, aroyl, halo, haloalkyl, haloalkoxy, hydroxy, alkoxy, alkylthioether, cycloalkyloxy, heterocylooxy, oxo, alkanoyl, aryl, arylalkyl, alkylaryl, heteroaryl, heteroarylalkyl, alkylheteroaryl, heterocyclo, aryloxy, alkanoyloxy, amino, alkylamino, arylamino, arylalkylamino, cycloalkylamino, heterocycloamino, mono- and di-substituted amino, alkanoylamino, aroylamino, aralkanoylamino, thiol, alkylthio, arylthio, arylalkylthio, cycloalkylthio, heterocyclothio, alkylthiono, arylthiono, arylalkylthiono, alkylsulfonyl, arylsulfonyl, arylalkylsulfonyl, sulfonamido, nitro, cyano, carboxy, carbamyl, alkoxycarbonyl and guanidino.

20-28. (Canceled)

REMARKS

Upon entry of the presently made amendments, claims 1-3, 7 and 9-19 will be pending. Claims 4-6 and 8 have been canceled without prejudice.

Claims 1, 9, 16 and 19 have been amended to recite groups that can be substituents. Support for these amendments is found in the specification as filed at least at page 9, line 21 to page 10, line 7.

Claims 1, 9, 16 and 19 have been further amended to recite a more focused class of compounds. Support for these amendments is found in the specification as filed at least at page 25, lines 8-11 and page 21, line 20 to page 23, line 6.

Claims 1, 9 and 19 have been further amended to recite that the disease or cancer to be treated or cancer cell to be inhibited is associated with a nonsense mutation in the p53 gene. Support for these amendments is found in the specification as filed at least at page 6, lines 27-29.

Claims 1, 9 and 16 have been further amended to recite methods of treatment. Support for these amendments is found in the specification as filed at least at page 7, lines 26-27.

No new matter has been added.

Applicants reserve their right to prosecute the subject matter of any canceled or amended claim or any unclaimed subject matter in one or more divisional, continuation or continuation-in-part applications.

I. The Rejection of Claims 1-6 and 9-19 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-6 and 9-19 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, the Examiner has stated that these claims are indefinite because the substituents of substituted groups are not defined. Without acquiescing in the rejection and solely to expedite prosecution, Applicants have amended claims 1, 9, 16 and 19 to recite particular groups that can be substituents.

Accordingly, Applicants respectfully submit that the amended claims satisfy the requirements set forth in 35 U.S.C. § 112, second paragraph, and that the rejection of claims 1-6 and 9-19 as being indefinite should be withdrawn.

II. The Rejection of Claims 1-6 and 9-19 Under 35 U.S.C. § 112, First Paragraph

Claims 1-6 and 9-19 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

While acknowledging that the specification is enabling for a method comprising administering the species recited in claim 7, the Examiner has stated that the specification does not reasonably provide enablement for a method comprising administering any compound of formula I.

Without acquiescing in this rejection and solely to expedite prosecution of the present application, Applicants have amended claims 1, 9, 16 and 19 to recite a more focused class of compounds. Applicants respectfully submit that the amended claims are reasonably enabled at least by the *in vitro* and *in vivo* nonsense mutation suppression data in connection with clitocine set forth in Examples 5.2.7-5.2.11 and the *in vitro* data in connection with additional compounds that are representative of this class set forth in Table 1 of the specification as filed.

Accordingly, Applicants respectfully submit that the pending claims satisfy the enablement requirement set forth in 35 U.S.C. § 112, first paragraph, and that the rejection of claims 1-6 and 9-19 for lack of enablement has been overcome and should be withdrawn.

III. The Rejection of Claims 1-3, 6, 9-11 and 18-19 Under 35 U.S.C. § 103(a)

Claims 1-3, 6, 9-11 and 18-19 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Sanghvi *et al.*, 1989, *J. Med. Chem. 32*:629-637 ("Sanghvi"). In particular, the Examiner has stated that Sanghvi discloses certain compounds that fall with the limits of the generic structure (I) in instant claim 1 and that the compounds are said to possess antitumor properties. Applicants respectfully traverse this rejection.

As discussed above, claims 1, 9 and 19 have been amended to recite a more focused class of compounds. In particular, the compounds are those wherein the variable Z is an optionally substituted pyrimidine, pyridine or phenyl group. In contrast, the compounds of Sanghvi contain a pyrimido[5,4-d]pyrimidine group.

Applicants respectfully submit that Sanghvi does not provide the requisite suggestion or motivation to modify the compounds described therein to arrive at the compounds of the amended method of use claims. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *In re Grabiak*, 769 F.2d 729, 732 (Fed. Cir. 1985).

Accordingly, Applicants respectfully submit that the rejection of claims 1-3, 6, 9-11 and 18 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

IV. The Rejection of Claims 1-15 and Under 35 U.S.C. § 112, First Paragraph

Claims 1-15 and 19 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

While acknowledging that the specification is enabling for the treatment of certain specific p53-associated tumors, the Examiner has stated that the specification does not reasonably provide enablement for the treatment of every type of cancer in existence.

Without acquiescing in this rejection and solely to expedite prosecution of the present application, Applicants have amended claims 1, 9 and 19 to recite that the disease or cancer to be treated or cancer cell to be inhibited is associated with a nonsense mutation in the p53 gene. Applicants respectfully submit that amended claims 1, 9, 19 and claims that depend therefrom, which are directed to more focused methods comprising the administration of a more focused class of compounds, are reasonably enabled at least by the data set forth in connection with clitocine and p53 in Examples 5.2.7-5.2.11 and the *in vitro* nonsense mutation suppression data in connection with additional compounds set forth in Table 1.

Accordingly, Applicants respectfully submit that the pending claims satisfy the enablement requirement set forth in 35 U.S.C. § 112, first paragraph, and that the rejection of claims 1-15 and 19 for lack of enablement has been overcome and should be withdrawn.

V. The Rejection of Claims 1-18 Under 35 U.S.C. § 112, First Paragraph

Claims 1-18 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

Applicants disagree with the Examiner's reasoning and respectfully submit that because compounds in the pending method of use claims are, without being limited by theory, believed to derive their therapeutic activity from their ability to suppress nonsense mutations, and such nonsense mutations are genetic mutations for which a patient can be screened, one skilled in the art could practice the claimed invention to prevent diseases associated with a nonsense mutation.

However, without acquiescing in the rejection and solely to expedite prosecution of the present application, claims 1, 9 and 16 have been amended to recite methods of treatment. Applicants acknowledge the Examiner's indication that the practice of administering a

therapy to a patient at risk for a disorder in order to reduce the likelihood or severity of the disorder is considered to be within the definition of the term "treatment."

In view of the above discussion and amendments to the claims, Applicants respectfully submit that the amended claims satisfy the enablement requirement set forth in 35 U.S.C. § 112, first paragraph, and that the rejection of claims 1-18 for lack of enablement should be withdrawn.

VI. The Rejection of Claims 1-19 Under 35 U.S.C. § 103(a)

Claims 1-19 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,324,731 to Kaddurah-Daouk *et al.* ("Kaddurah-Daouk"). Applicants respectfully traverse this rejection.

As noted by the Examiner, Kaddurah-Daouk discloses methods of inhibiting the growth, transformation and/or metastasis of mammalian cells in which activity of at least one purine metabolic enzyme is elevated. Indeed, the entire focus of Kaddurah-Daouk is the use of certain compounds as inhibitors of purine metabolic enzyme activity, message level, expression or interaction with other viral or cell products (*see* Kaddurah-Daouk, col. 2, line 64 to col. 3, line 11). In other words, Kaddurah-Daouk only teaches the use of certain compounds to decrease enzyme activity. There is no discussion or suggestion in Kaddurah-Daouk of the use of any compound to suppress a nonsense mutation to promote the expression of a gene product.

Applicants respectfully disagree with the Examiner's reasoning that one of ordinary skill in the art would find it obvious from the disclosure of Kaddurah-Daouk to treat a cancer associated with a loss of p53 with any compound, let alone clitocine. Rather, the key marker that Kaddurah-Daouk points to is purine metabolic enzyme activity. Thus, regardless of the status of p53 in a patient's cells, if elevated purine metabolic enzyme activity is not detected, there would be no motivation to administer any compound of Kaddurah-Daouk. In other words, if it was determined that tumor cells from a patient were not characterized by elevated activity of a purine metabolic enzyme, there would be no motivation to administer clitocine, or any compound of Kaddurah-Daouk, regardless of the level of p53 expression. *In re Vaeck* at 493. In addition, there would be no expectation of success with respect to the treatment of such a disease which was not shown to be characterized by elevated activity of a purine metabolic enzyme. *Id.*

Furthermore, the Examiner has stated that the teaching of Kaddurah-Daouk that certain compounds which are inhibitors of a purine metabolic enzyme (*i.e.*, creatine kinase) lack anti-tumor activity does not provide a reason to doubt that the recited compounds,

including clitocine, are functional embodiments. Applicants respectfully disagree. Kaddurah-Daouk teaches that the compounds described therein have anti-tumor activity because of their ability to inhibit the activity of a purine metabolic enzyme, such as creatine kinase. Thus, Applicants respectfully submit that a showing that certain creatine kinase inhibitors lack anti-tumor activity does indeed provide a reason to doubt that other kinase inhibitors possess anti-tumor activity and, in fact, teaches away from their use as anti-tumor agents.

For these reasons, Applicants respectfully submit that the pending claims are not obvious over Kaddurah-Daouk.

Accordingly, Applicants respectfully submit that the rejection of claims 1-19 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

VI. The Provisional Double Patenting Rejection

Claims 1-19 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-10 of co-pending Application No. 11/048,659 (the "'659 application). Per M.P.E.P § 804, a provisional double patenting rejection should continue to be made unless it is the sole remaining rejection in one of the applications. Upon entry of the presently made amendment and remarks, Applicants believe that the sole remaining rejection in the present application will be the provisional double patenting rejection over the '659 application. Accordingly, Applicants respectfully request that the provisional double patenting rejection over the '659 application be withdrawn. Applicants will then consider filing a terminal disclaimer in the '659 application over the present application.

Conclusion

Applicants respectfully request that the above amendments and remarks be entered in the present application file. No fee is believed to be due in connection with this Response other than that in connection with the Petition for Extension of Time; however, in the event that any additional fee is due, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Anthony M. Insogna, Reg. No. 35,203
By: Michael J. Bruner, Reg. No. 47,458

Date: April 19, 2007

By: Michael J. Bruner (Reg. No. 47,458)
JONES DAY
222 East 41st Street
New York, New York 10017
(404) 581-8614

For: Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
12265 El Camino Real, Suite 200
San Diego, California 92130
(858) 314-1130

Enclosures